

REMARKS

Claims 28-49 are pending in the present application and at issue. Claim 28 has been amended to delete the phrase "has less than 10% residual activity when inhibited with a molar excess *Streptomyces subtilisin* inhibitor" and to incorporate the subject matter of claim 29. The Office Action mailed June 15, 2004 states that this property is "an inherent property of subtilisins" and therefore redundant. Claim 29 has been amended to add that "the activity of the protease is at least 45% of the reference activity," as supported by page 7, line 21 of the specification.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 14 and 15 under 35 U.S.C. 102

Claims 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiller (U.S. Patent No. 4,239,750), Hiller (U.S. Patent No. 4,225,584), Hiller (U.S. Patent No. 4,218,437), or Lehmann et al. (U.S. Patent No. 4,062,732). This rejection is respectfully traversed.

The Hiller and Lehmann patents disclose animal feeds comprising an antibiotic and a protease. The protease can be produced from *Bacillus licheniformis*, *Bacillus natta* [sic, *natto*], and *Bacillus subtilis*. Furthermore, preferred proteases are acid proteases, e.g., from *Aspergillus niger* or those described in U.S. Patent Nos. 3,674,644 and 3,677,898. Particularly preferred proteases are from the genus *Trametes*, or from *Rhizopus rhizopodiformis* (described by Lehmann in U.S. Patent No. 4,062,732).

Enclosed is a Declaration under 37 C.F.R. 1.132 of Peter Rahbek Østergaard, which describes experiments to determine if subtilisins derived from *Bacillus subtilis* and *Bacillus licheniformis* are acid stable. As explained in the Declaration, *natto* is no longer considered a species of *Bacillus*, but a variant of *Bacillus subtilis*. Therefore, a strain of *Bacillus subtilis* var. *natto* was also used in the experiments.

The results described in the Declaration demonstrate that none of the *Bacillus subtilis* and *Bacillus licheniformis* subtilisins are acid-stable according to the definition of the instant application.

With respect to the other proteases disclosed in the Hiller and Lehmann patents, i.e., the *Rhizopus rhizopodiformis* CBS 227.75 protease, the *Aspergillus niger* protease and the *Penicillium* and *Rhodotorula* proteases described in U.S. Patent Nos. 3,674,644 and 3,677,898, neither is a subtilisin.

Thus, the Hiller and Lehmann patents do not disclose an animal feed additive comprising a protease which is both a subtilisin and acid-stable, as claimed herein.

The Office Action also states that "The instant disclosure does not define what is meant by a subtilisin...." This is respectfully traversed.

The instant specification defines a subtilisin as a serine protease of Clan SB according to the Handbook of Proteolytic Enzymes (see pages 3 and 4 of the specification).

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102. Applicants respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 14-16 under 35 U.S.C. 103

Claims 14-16 are rejected under 35 U.S.C. 103 as being unpatentable over Hiller (U.S. Patent No. 4,239,750), Hiller (U.S. Patent No. 4,225,584), Hiller (U.S. Patent No. 4,218,437) or Lehmann et al. (U.S. Patent No. 4,062,732) in view of Outtrup et al. (U.S. Patent No. 5,597,720). This rejection is respectfully traversed.

The Hiller and Lehmann patents are discussed in Section I. As noted above, neither patent discloses the use of an acid-stable subtilisin in animal feed.

Furthermore, of these four patents, the only patent to test the use of a protease alone in animal feed is U.S. Patent No. 4,218,437 (Hiller). In particular, Hiller states at column 5, lines 36-46:

The above two examples demonstrate that the addition of the antibiotic Virginiamycin at a level of either 7.5 ppm or 15 ppm slightly improves both the end weight and the feed utilization, whereas the addition of the acid proteases at a level of 0.45 mTU/gm scarcely effects the end weight or feed utilization. Completely unexpectedly, a combination of both causes an effect which is more than additive (emphasis added)....

The only advantage to using a protease in animal feed described in Hiller is in the presence of an antibiotic.

The instant specification demonstrates that the use of proteases which are both subtilisins and acid-stable in animal feed result in significantly improved weight gain and feed conversion than subtilisins which are not acid-stable.

In particular, Example 4 of the instant application describes an *in vitro* testing of a subtilisin of the invention (the protease derived from *Bacillus* sp. NCIMB 40484) and four subtilisins which are not acid-stable (ALCALASE™, subtilisin Novo, subtilisin Novo (Y217L), and SAVINASE™). The results show that acid-stable subtilisins of the invention have a significantly better effect on

protein solubilization than the other subtilisins. These results were obtained using animal feed containing an acid-stable protease without any antibiotic.

Furthermore, Example 10 of the instant application describes an *in vivo* trial of the protease derived from *Bacillus sp.* NCIMB 40484. The results show that the use of the protease of the present invention resulted in a statistically significant improvement of feed conversion. These results were obtained using animal feed containing an acid-stable protease without any antibiotic.

In addition, Examples 3 and 9 demonstrate that acid-stable subtilisins degrade the insoluble parts of Soy Bean Meal (SBM) significantly more than proteases I and II, which are acid-stable aspartate proteases, also in the absence of an antibiotic.

Since none of these results could have been predicted from the prior art, the results are surprising and unexpected, especially since the primary references require the presence of both a protease and an antibiotic to improvement in feed utilization.

The secondary references merely disclose acid-stable subtilisins, but not their use in animal feed.

Applicants therefore submit that the references, alone and in combination, do not render obvious animal feed comprising an acid-stable subtilisin.


For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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